IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Reinhard NUBBEMEYER et al.

: Group Art Unit.: 1616

Serial No.: 10/522,169 : Examiner: CHUI, Mei Ping

Filed: : January 24, 2005

Title: COMPOSITION CONTAINING AN ANDROGENOUS 11 BETA-HALOGEN STEROID AND A PROGESTATIONAL HORMONE, AND MALE CONTRACEPTIVE BASED ON SAID COMPOSITION

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

I, Dr. NUBBEMEYER, Reinhard, being duly warned, declare that:

I am a co-inventor of the above-captioned application and am, therefore, familiar with the invention described therein and with the grounds for rejection made against the claims by the U.S. Patent and Trademark Office. My expertise for making this declaration is further demonstrated in the CV attached to my previous declaration.

I am a citizen of Germany , residing in Berlin, Germany.

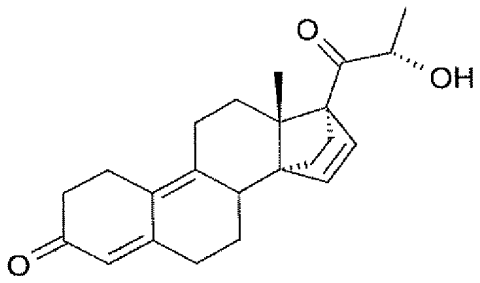
If a patent issues from this application and if it is decided by the assignee to pursue a commercial product falling under its claims and if such a commercial product is approved by FDA and sold in the US, then under German law, I and the other inventors will receive some remuneration derived from such sales.

I am familiar with the Office Action issued on April 30, 2009, and with the references cited therein.

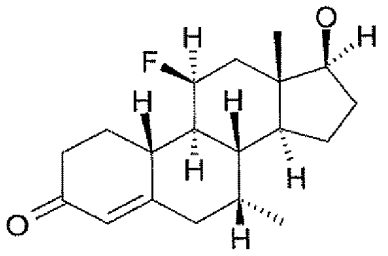
I have either performed or supervised the following experiments. All experiments had been performed in male rats or male castrated rats ($N \geq 6$ each group).

The following compounds were used in the experiments.

The gestagen recited in the claims (hereinafter identified as gestagen or ZK 187226), i.e.:

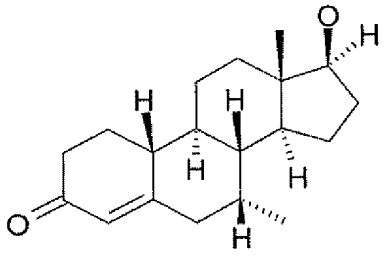


The compound recited in the claims 11β-fluoro-17β-hydroxy-7α-methyl-estr-4-en-3-one (hereinafter eF-MENT or ZK 224312), i.e.:



, and

The compound, which is otherwise the same as the compound eF-MENT, except for the absence of the 11β-fluoro substituent (hereinafter MENT or ZK 31618), i.e.:



In particular the androgenic and anabolic profile of MENT is almost identical with the one of eF-MENT as it can be seen when comparing the effect of the compounds on the organ weights (determined by a modified Hershberger assay[1], see attachments 1 and 2). As the effect on testosterone levels and organ weights come along with the androgenic properties, values measured for MENT can be used as surrogate values also for eF-MENT, as explained in (2).

(1) The studies GF1999.0611, GF2001.0006 and GF2001.0356 are tests on spermatogenesis. GF1999.0611 investigated the effect of the Gestagen (ZK 187226), GF2001.0006 the effect of MENT (ZK 31618) and GF2001.0356 the effect of the combination of the Gestagen (ZK

[1] Hershberger L, Shipley E, Meyer R. 1953. Myotrophic activity of 19-nortestosterone and other steroids determined by modified levator ani muscle method. *Proc. Soc. Exp. Biol. Med.* **83**: 175–180.

187226) and eF-MENT (ZK 224312).

In this test adult, intact male rats were treated 6 weeks with either vehicle or different doses of the test compound(s). Blood (to check the hormonal status) was taken after 2 and 4 weeks and at the end of the experiment. Organ weights and sperm were collected at the end of the experiment. In the studies provided below Testosterone (attachments 3.1.1, 3.1.2; 3.2.1, 3.2.2; 3.3.1 and 3.3.2) and LH-serum (attachments 4.1.1, 4.1.2; 4.2.1, 4.2.2; 4.3.1 and 4.3.2) levels were measured. In addition the number of sperms (which is - at the end of the day - the most relevant factor, if male contraception is intended) and additionally the sperm motility has been determined (see attachment 5.1, 5.2, and 5.3).

The testosterone concentration results demonstrate that each of the gestagen and MENT (as surrogate for eF-MENT) independently and generally in a dose dependent manner decreased the testosterone levels. As can be seen however, when a combination of the gestagen and eF-MENT is administered, the testosterone concentrations are much more significantly and much more than additively decreased, which is unexpected in view of what is known about these compounds and the effects thereof in the art.

For example, at 2 weeks, at a low dose of 1 mg of gestagen the testosterone level is about 1.8 nmol/L and at 0.015 mg of MENT the testosterone level is about 5.1 nmol/L. However, when a combination of the gestagen and eF-MENT at these doses are provided, the testosterone level of 6 out of 8 animals was below the limit of detection (i.e. 0.2 nmol/L). At all measured combinations and at all points in time of measurement the data demonstrate a significant and unexpected combined, i.e., synergistic, effect, which is much more than additive and much more than what one of skill would have expected. After 6 weeks of treatment low levels of testosterone were observed in the groups treated with the lower androgen dose. Nevertheless, these combinations were the most effective ones with respect to sperm number demonstrating that low peripheral androgen levels are tolerable in fertility control.

The LH levels are known to be more variable than testosterone. The LH-serum levels likewise demonstrate a synergistic effect to testosterone as part of the hormonal feedback loop. As can be seen, the effect of the gestagen alone on the LH-serum levels provides variable results. For MENT alone, the decrease follows a general dose dependent decrease. However, when a combination is administered, the combined effect is unexpectedly much more than additive again.

The principle of male contraception is to suppress the sperm production in the testis and to lower the sperm number/concentration as a consequence. The production and function of sperm is interdependent with testosterone production. The data demonstrate that the gestagen alone in a general dose dependent manner decreases the sperm count. The data also demonstrate that MENT (as surrogate for eF-MENT) alone does not lower in all doses the sperm count and the sperm motility at all. MENT (as surrogate for eF-MENT) is a very potent androgen replacing testosterone. However, when the combination of the gestagen and eF-MENT is administered, the sperm counts are much more significantly and much more than additively decreased, which is unexpected in view of what is known about these compounds and the effects thereof in the art.

The data on sperm motility demonstrate that MENT alone does not have an effect, and that a somewhat decreased motility is achieved with the combination at some dosages compared and at in the higher dosages of the gestagen alone. The main read-out of this experiment was the reduction of the sperm number, sperm motility is a minor read out in this type of experiment.

(2) To demonstrate that the data for MENT and eF-MENT would be considered comparable by one of skill in this art, organ weights data (prostate and seminal vesicle) are provided to establish that these compounds have the same or substantially the same pharmacological activity and/or profile, e.g., androgenic activity. As such, it would be accepted by one or skill in this art to correlate data obtained for MENT (attachment 1) with data on eF-MENT (attachment 2).

The test used is called "Hershberger Test." In this test juvenile castrated male rats are treated 7 days with vehicle, testosterone-propionate (ZK 4955) as reference and the test compounds, i.e. MENT or eF-MENT. At the end of the experiment the weight of the prostate gland, the seminal vesicles and the M. levator ani was determined to evaluate the androgenic and anabolic potency of the compounds.

In the diagrams below the activities for MENT (ZK31618) and for eF-MENT (ZK244312) have been measured for different doses (0.005, 0.015, 0,05 and 0.15 mg/kg and day for MENT and 0.015, 0,05 and 0.15 mg/kg and day for eF- MENT). The first 2 bars in the diagrams (Kontrolle = control and ZK 4955 dosed 1mg/kg/day subcutaneously) are always measured along for control purposes. The 1 mg/kg/day dose of testosterone propionate is the maintenance dose in this model (routinely used over years).

One of skill in the art would interpret these data on prostate and seminal vesicle weights as demonstrating only minor differences among MENT and eF-MENT, e.g., the results obtained across the board for both compounds in the respective tests stay within the range of error. As a further parameter, the effect on Musculus levator ani has been investigated. Results give information on anabolic virility. These data also confirm the similar pharmaceutical profiles and effects for MENT and eF-MENT. The adrenals were monitored in this experiment to detect potential side effects (glucocorticoid property), which was not observed for both androgens.

(3) In sum, one of skill in this art would conclude that both MENT and eF-MENT have the same or substantially the same pharmacological activity and/or profile. It would therefore be accepted by one or skill in this art to correlate data obtained for MENT with data on eF-MENT. As such, one of skill in this art would find the data establishing synergism (unexpected significant advantages) on the combination of eF-MENT with the gestagen of the claims versus the gestagen alone and MENT alone convincing evidence of synergism not expectable from what was known in the art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

25.11.2009
Date

R. Nubbemeyer
Dr. NUBBEMEYER, Reinhard

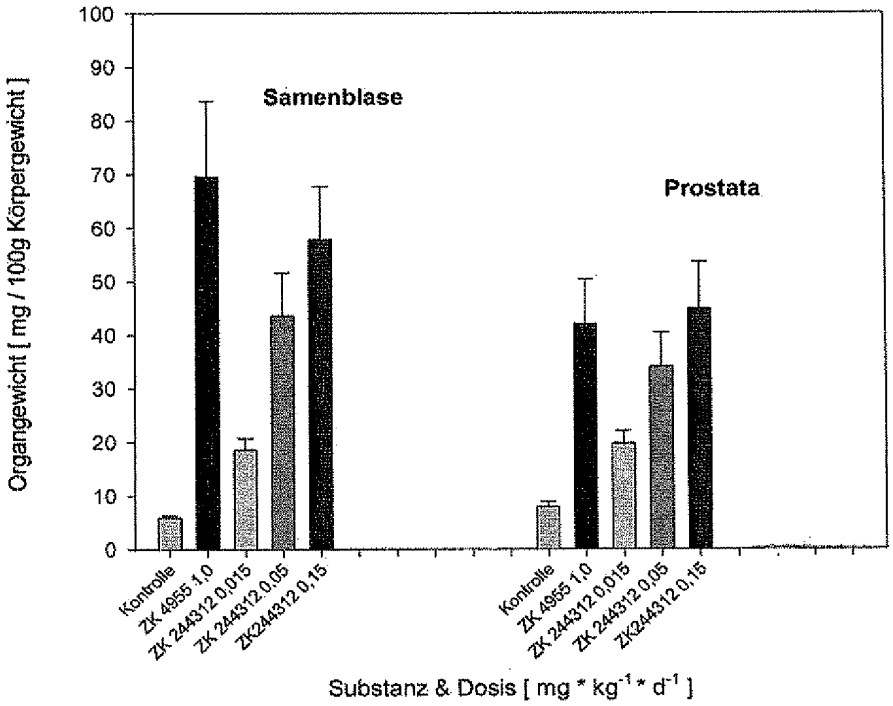
Klein/FKHT
20.02.01

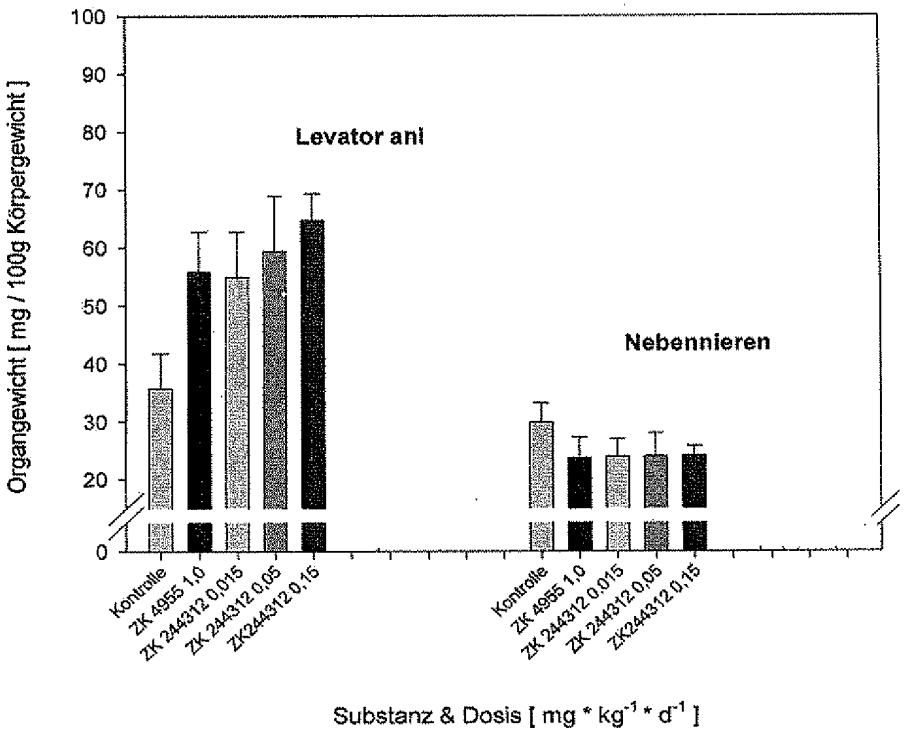
Schering AG
Research

GF 2001.0049

Graphische Darstellung der rel.Organgewichte vom Androgentest

(ZK 244312)



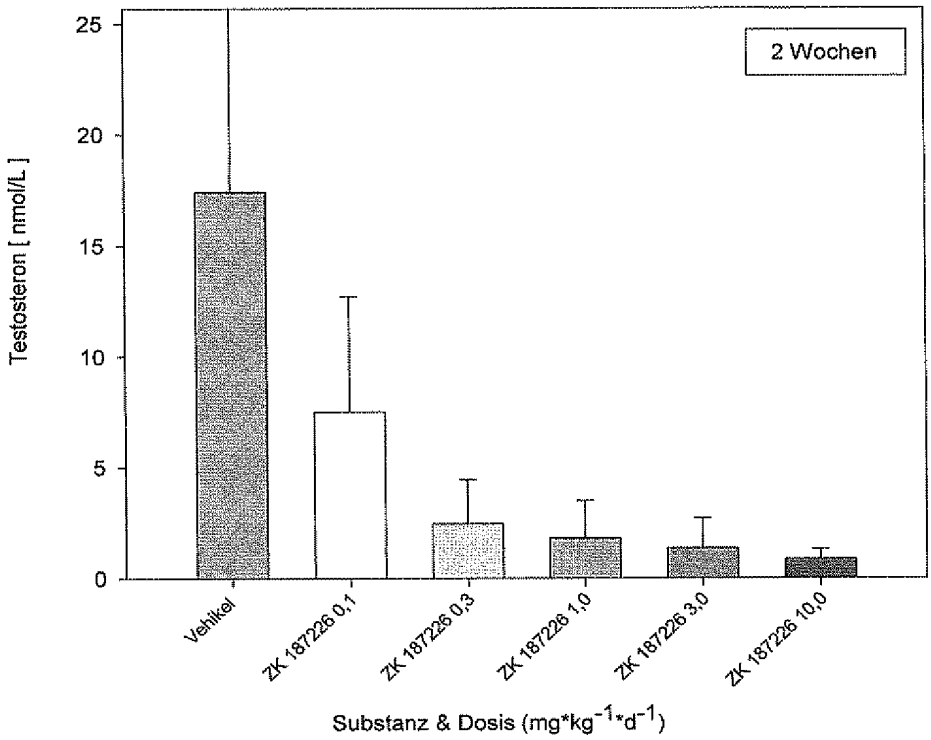


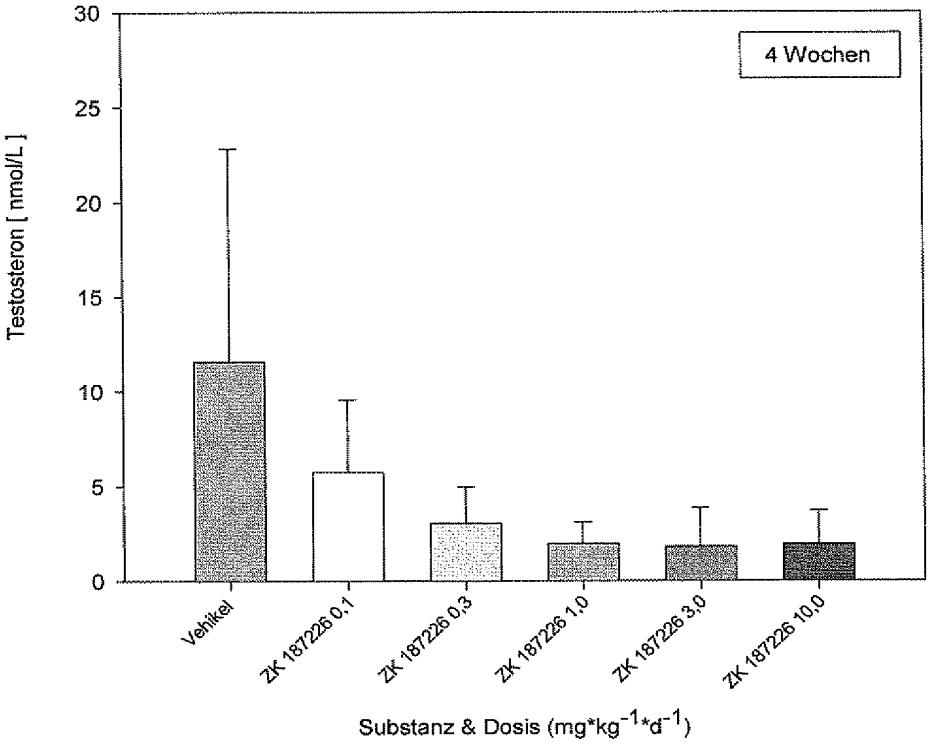
Marin/FKHT
29.02.00

Schering AG
Research

GF 1999.0611

Einfluß von ZK 187226 auf die Testosteron-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 2 und 4 Wochen bei s.c. Applikation



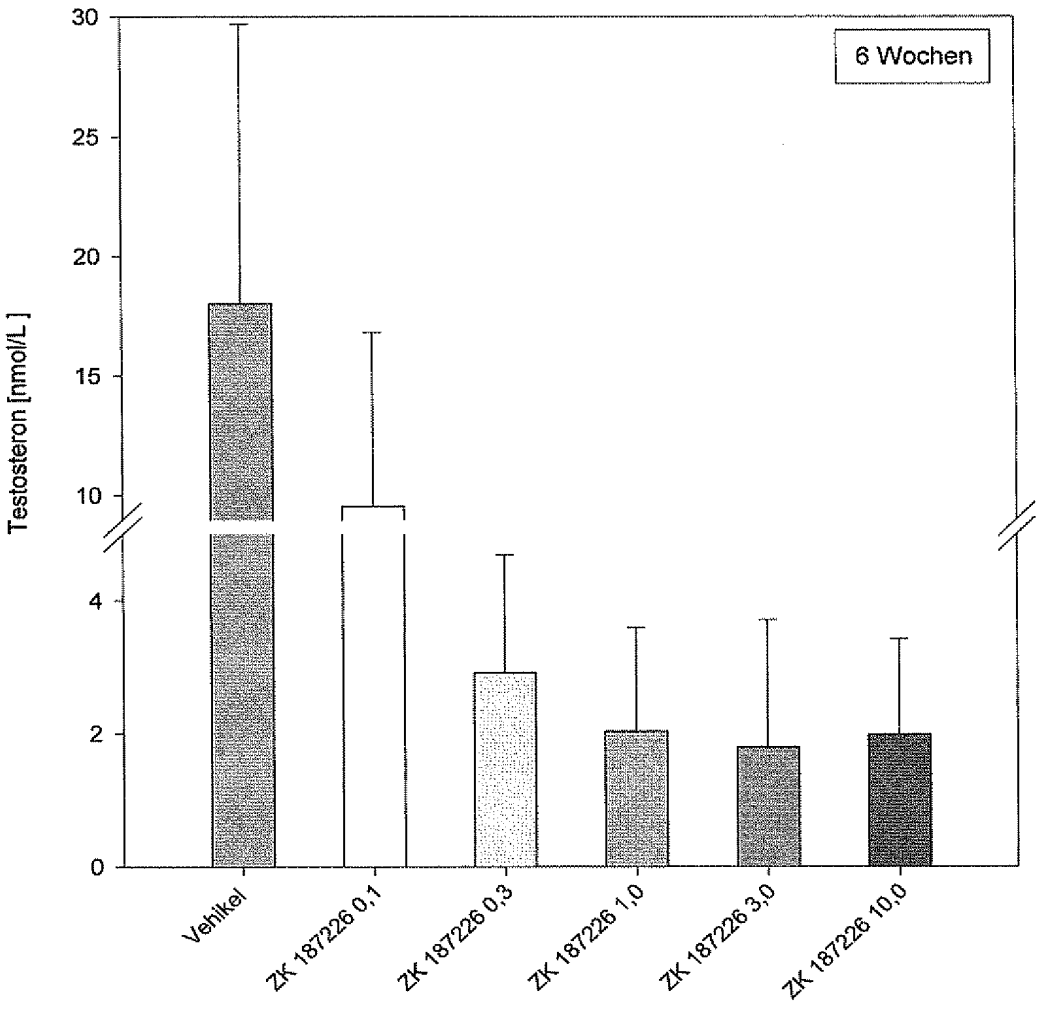


Marin/FKHT
29.02.00

Schering AG
Research

GF 1999.0611

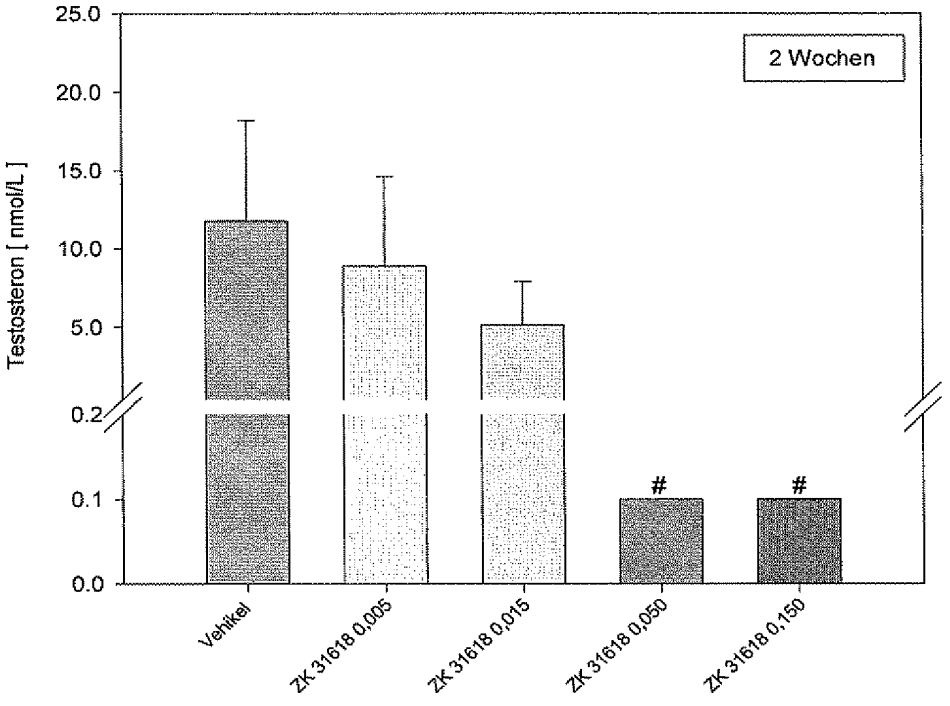
Einfluß von ZK 187226 auf die Testosteron-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 6 Wochen bei s.c. Applikation

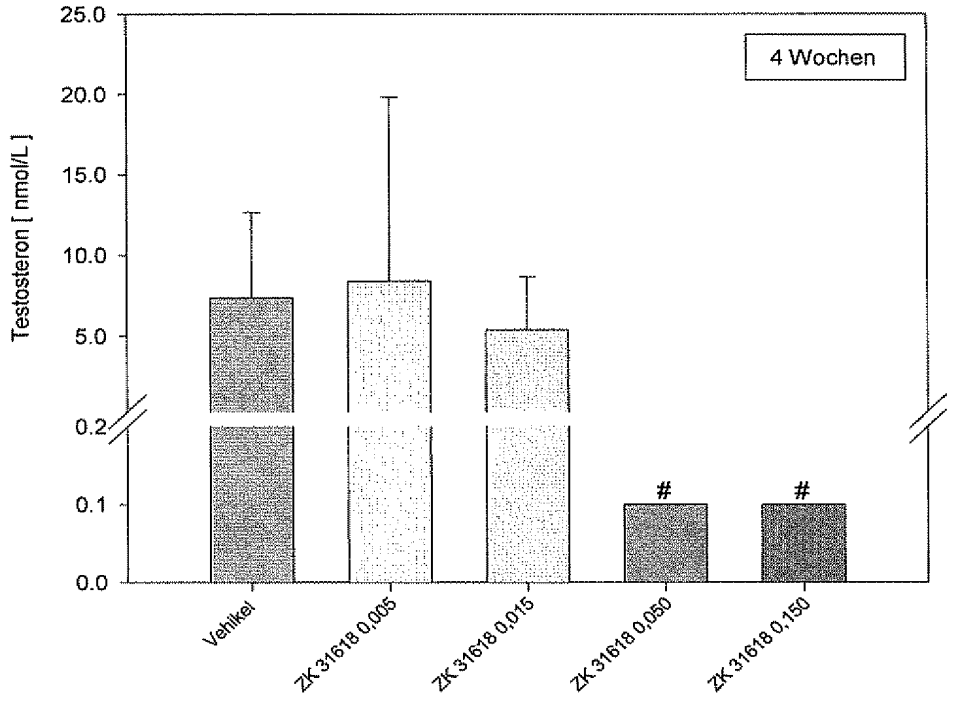


Schering AG
Research

GF 2001.0006

Einfluß von ZK 31618 (MENT) auf die Testosteron-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 2 und 4 Wochen bei s.c. Applikation





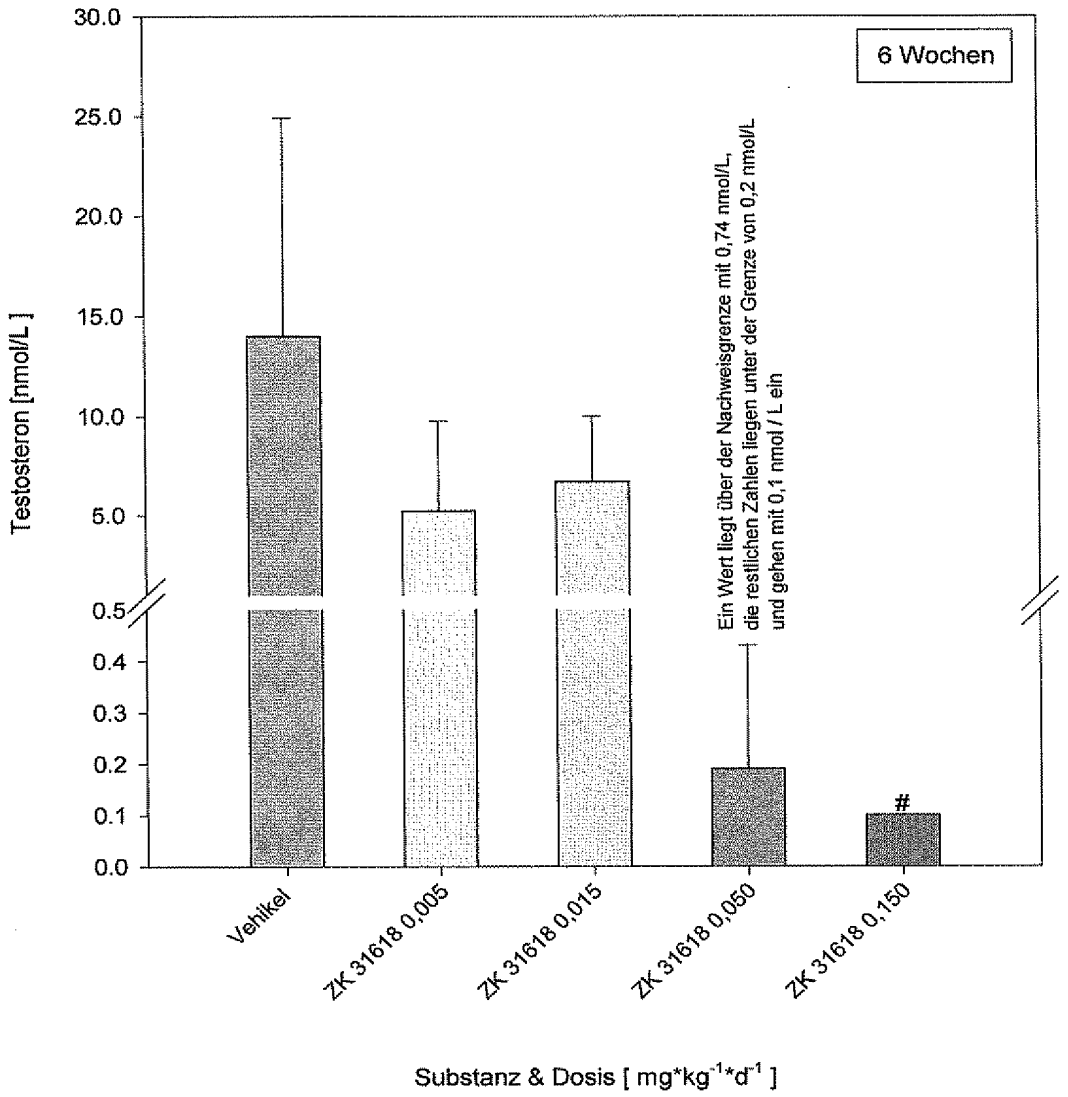
Werte liegen alle unter der Nachweisgrenze von 0,2 nmol/l. Sie werden mit der Hälfte dargestellt.

Klein/FKHT
03.05.2001

Schering AG
Research

GF 2001.0006

Einfluß von ZK 31618 (MENT) auf die Testosteron-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 6 Wochen bei s.c. Applikation

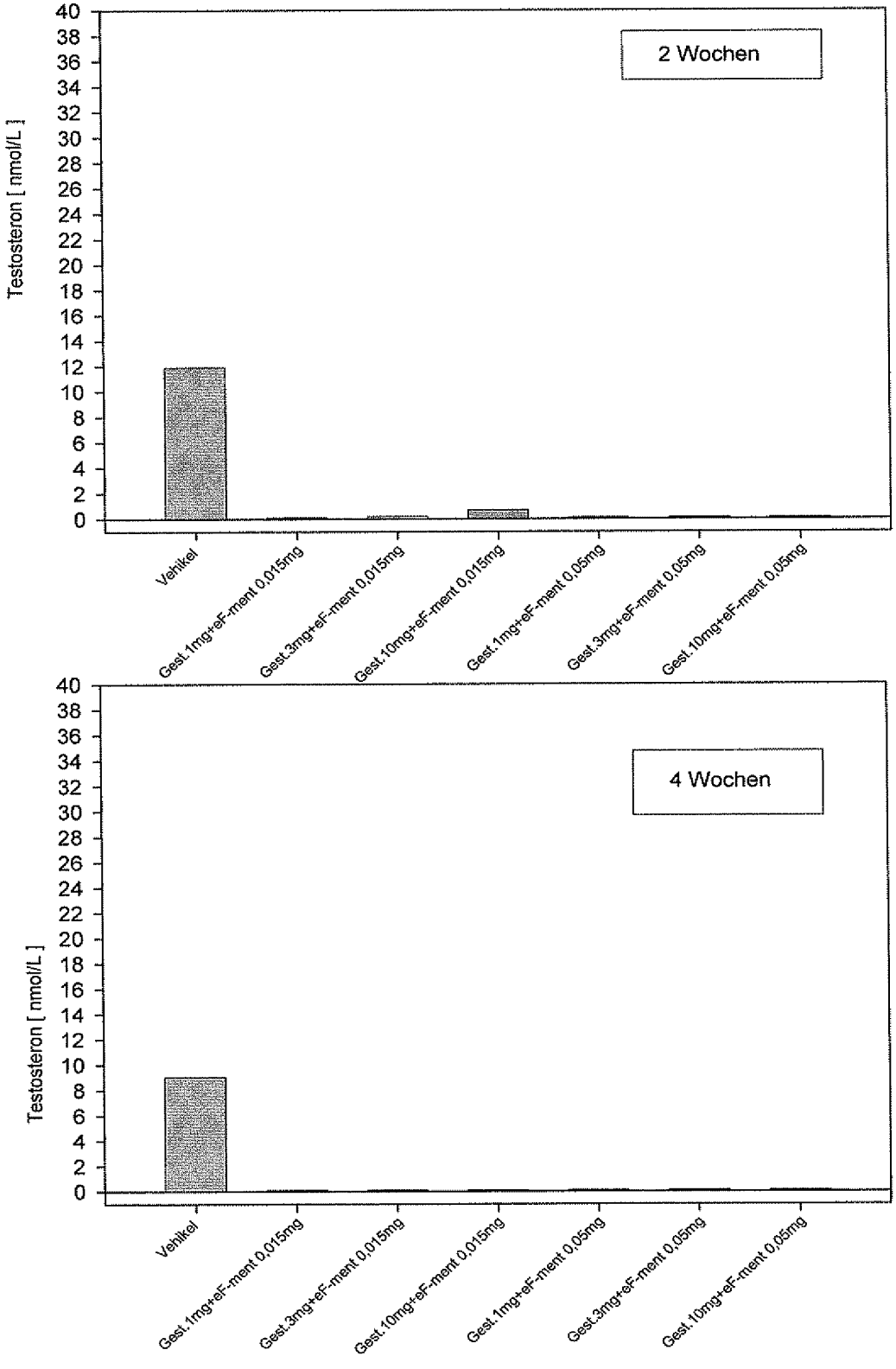


Werte liegen alle unter der Nachweisgrenze von 0,2 nmol/l. Sie werden mit der Hälfte dargestellt.

Efiloglu/FKHT
16.12.02

GF 2002.356

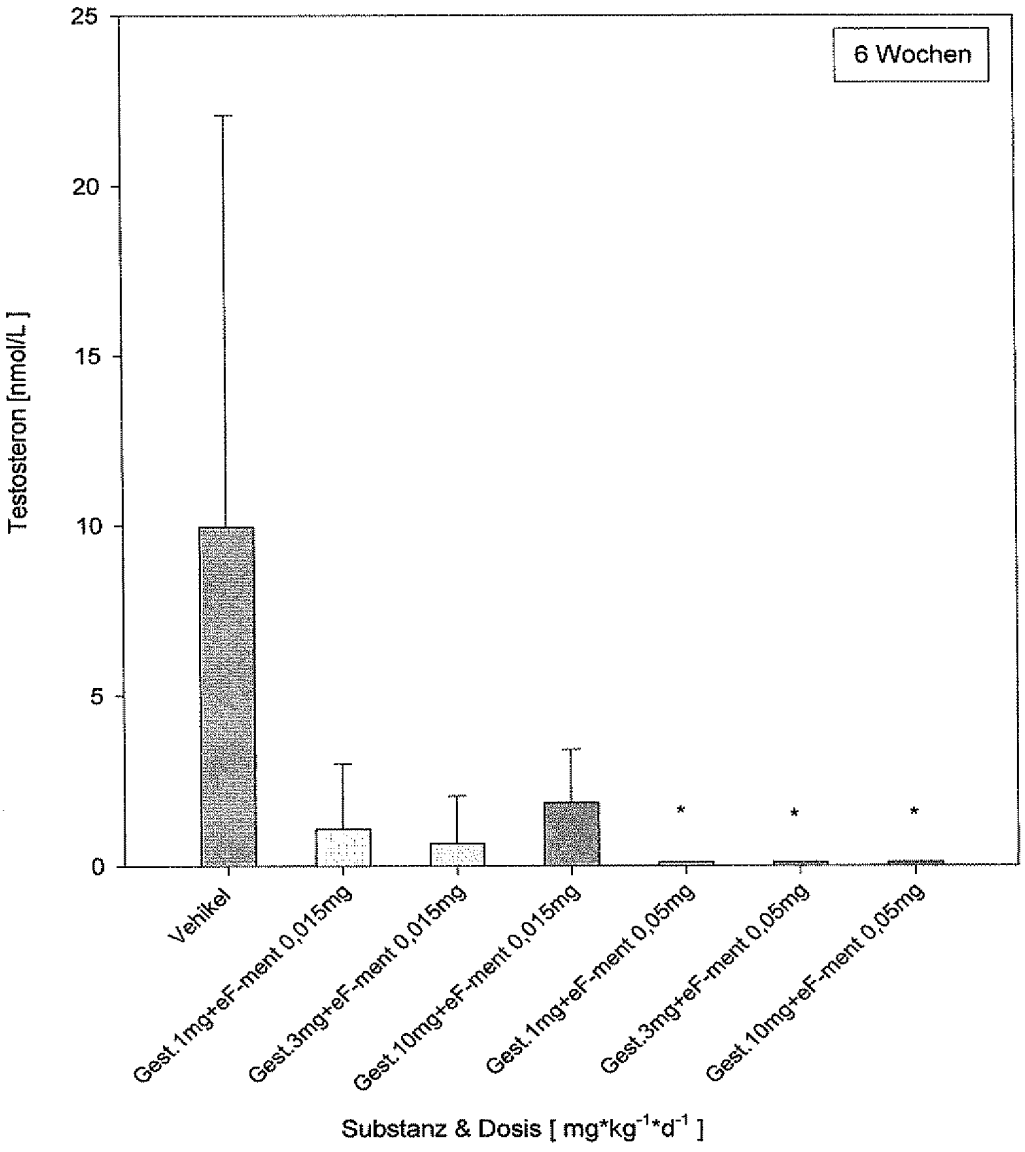
Einfluß von ZK 187.226(Gestagen) in Komb. mit ZK 244.312(eF-Ment)
auf die Testosteron-Konzentration
im Serum bei der männl. Ratte nach einem Behandlungszeitraum
von 2 und 4 Wochen bei s.c. Applikation
Werte als Median



Efiloglu/FKHT
16.12.02

GF 2002.356

Einfluß von ZK 187.226(Gestagen) in Komb. mit ZK 244.312(eF-Ment) auf die Testosteron-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 6 Wochen bei s.c. Applikation

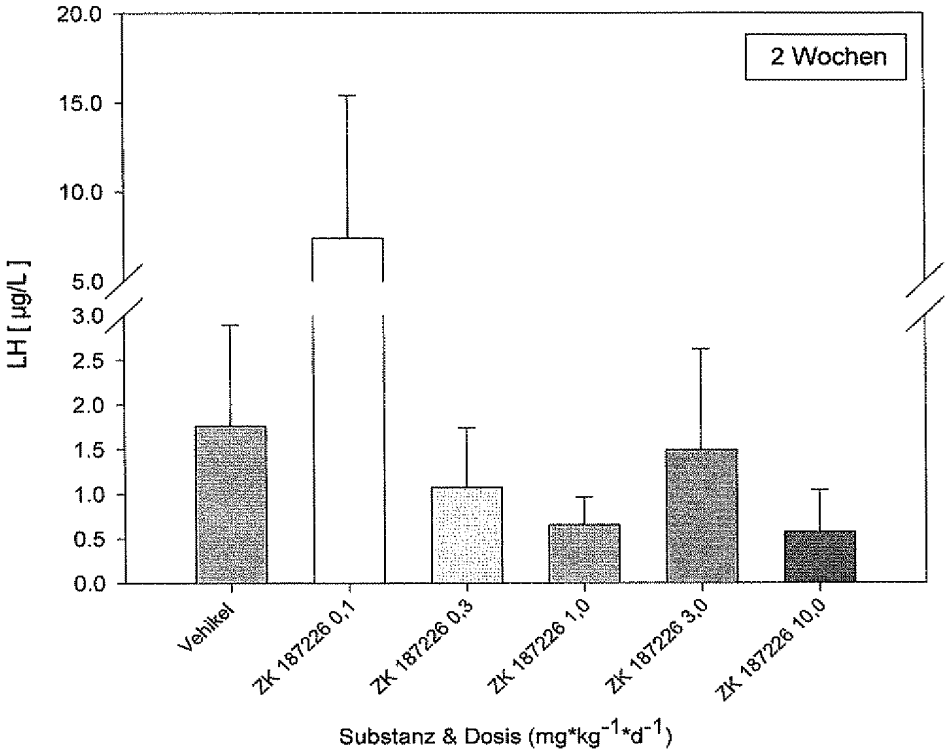


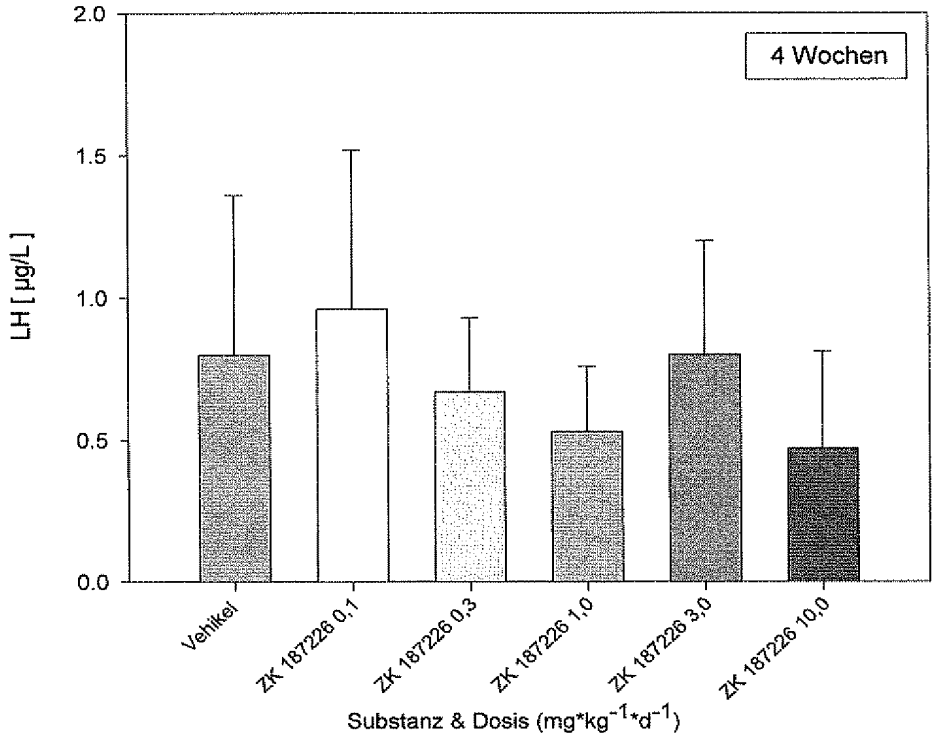
* alle Werte unter der Nachweisgrenze/halbe Nachweisgrenze berechnet und dargestellt

Schering AG
Research

GF 1999.0611

Einfluß von ZK 187226 auf die LH-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 2 und 4 Wochen bei s.c. Applikation



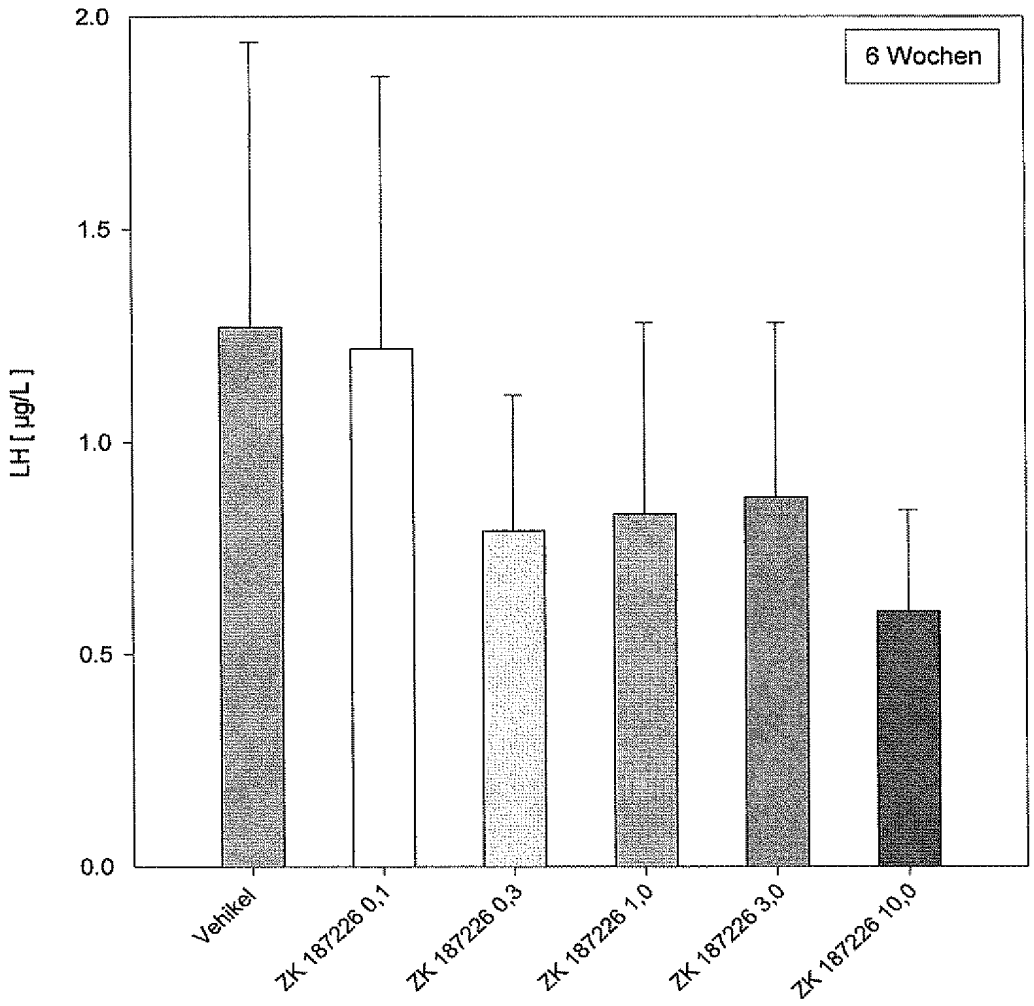


Marin/FKHT
29.02.00

Schering AG
Research

GF 1999.0611

Einfluß von ZK 187226 auf die LH-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 6 Wochen bei s.c. Applikation

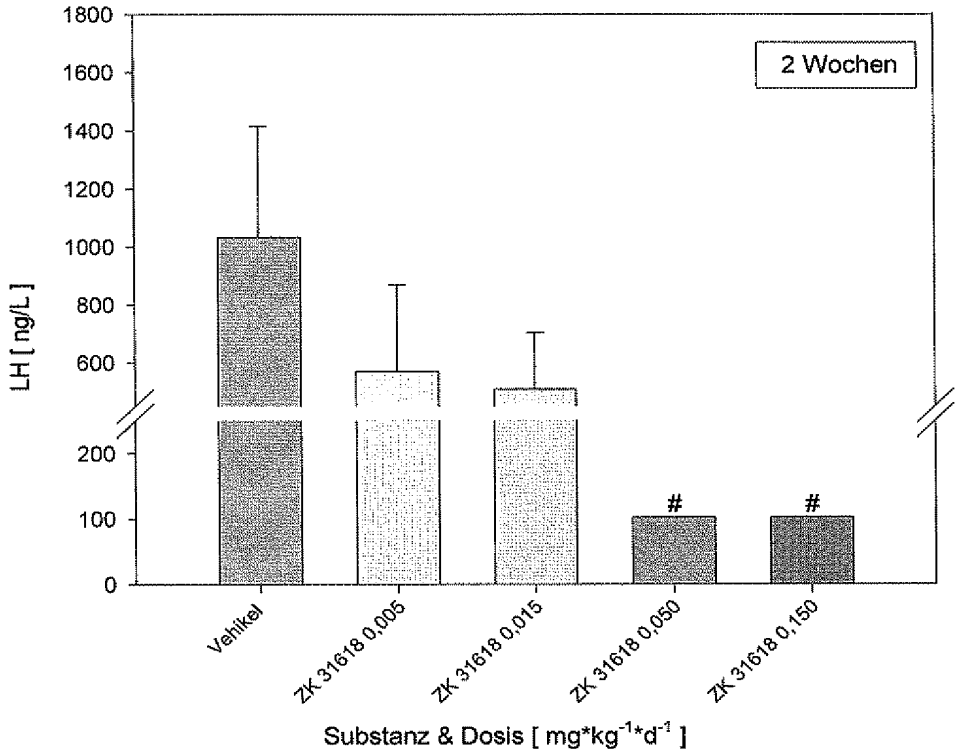


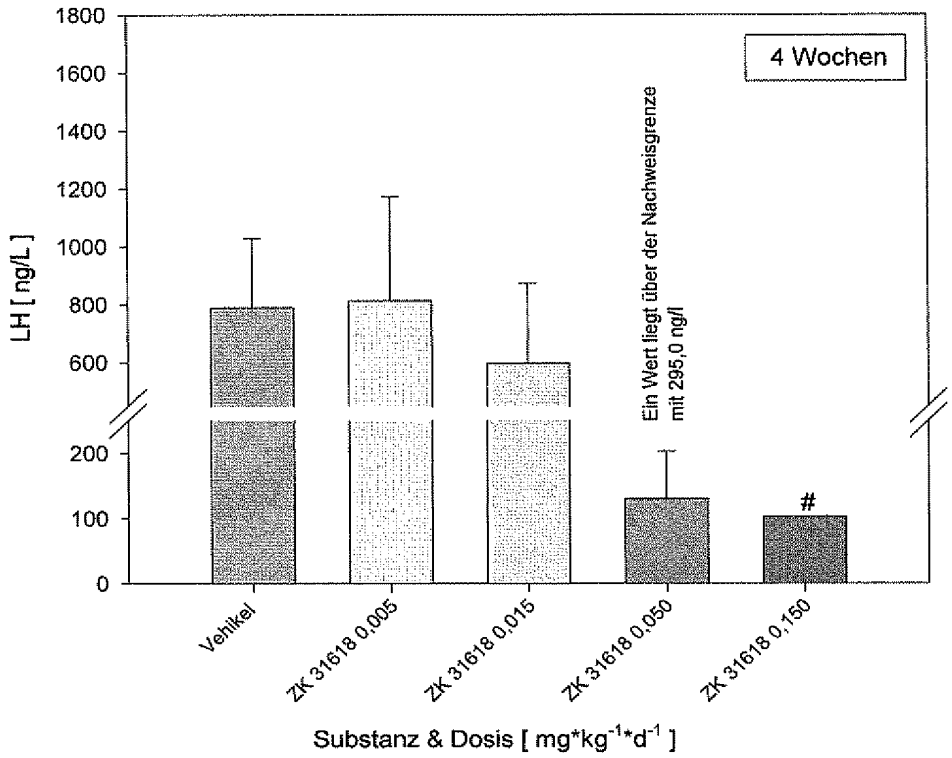
Klein/FKHT
23.05.01

Schering AG
Research

GF 2001.0006

Einfluß von ZK 31618 auf die LH-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 2 und 4 Wochen bei s.c. Applikation





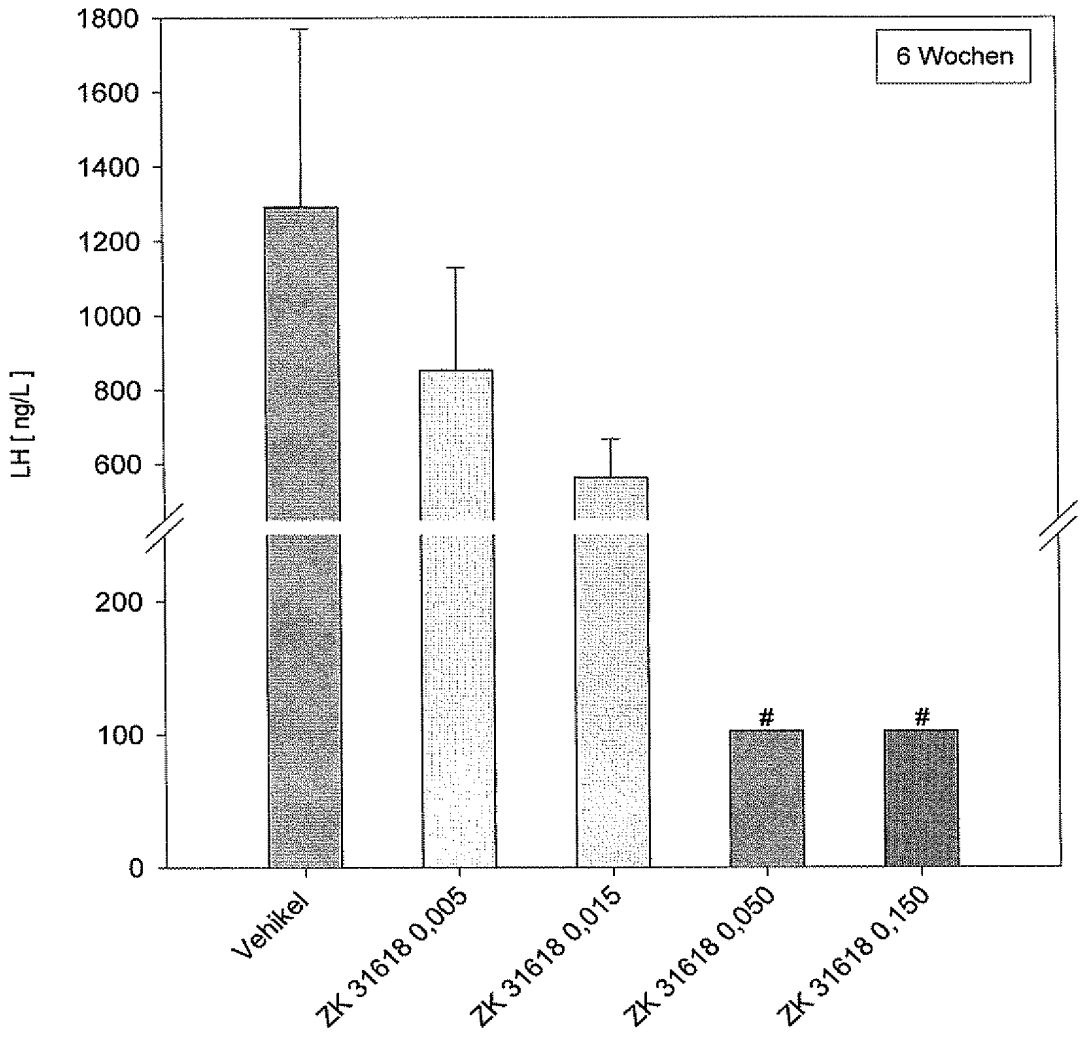
Werte liegen alle unter der Nachweisgrenze von 205 ng/L. Sie werden mit der Hälfte dargestellt.

Klein/FKHT
23.05.01

Schering AG
Research

GF 2001.006

Einfluß von ZK 31618 auf die LH-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 6 Wochen bei s.c. Applikation

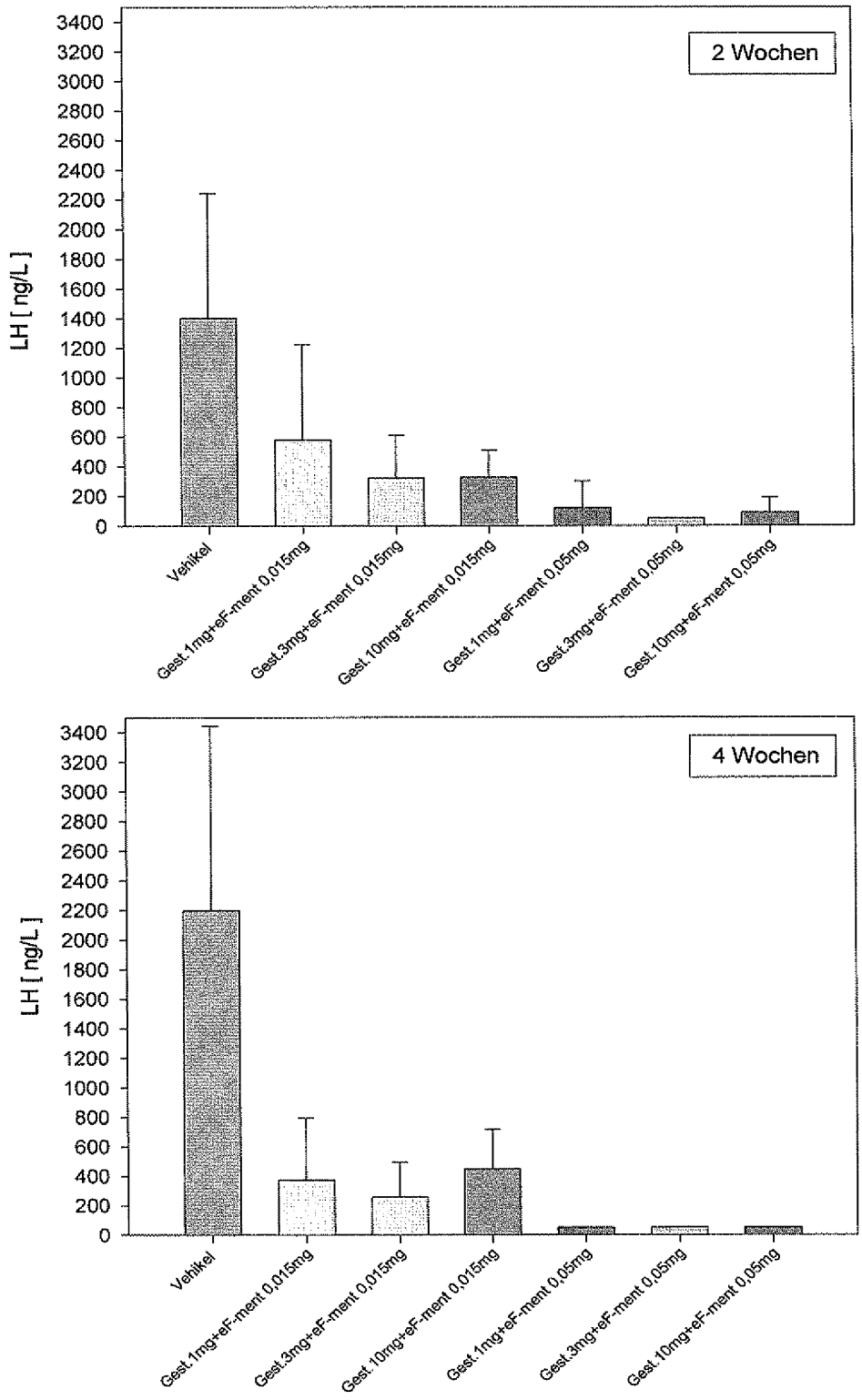


Werte liegen alle unter der Nachweisgrenze von 205 ng/L. Sie werden mit der Hälfte dargestellt.

Efiloglu/FKHT
28.11.02

GF 2002.356

Einfluß von ZK 187.226(Gestagen) in Komb. mit ZK 244.312(eF-Ment) auf die LH-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 2 und 4 Wochen bei s.c. Applikation



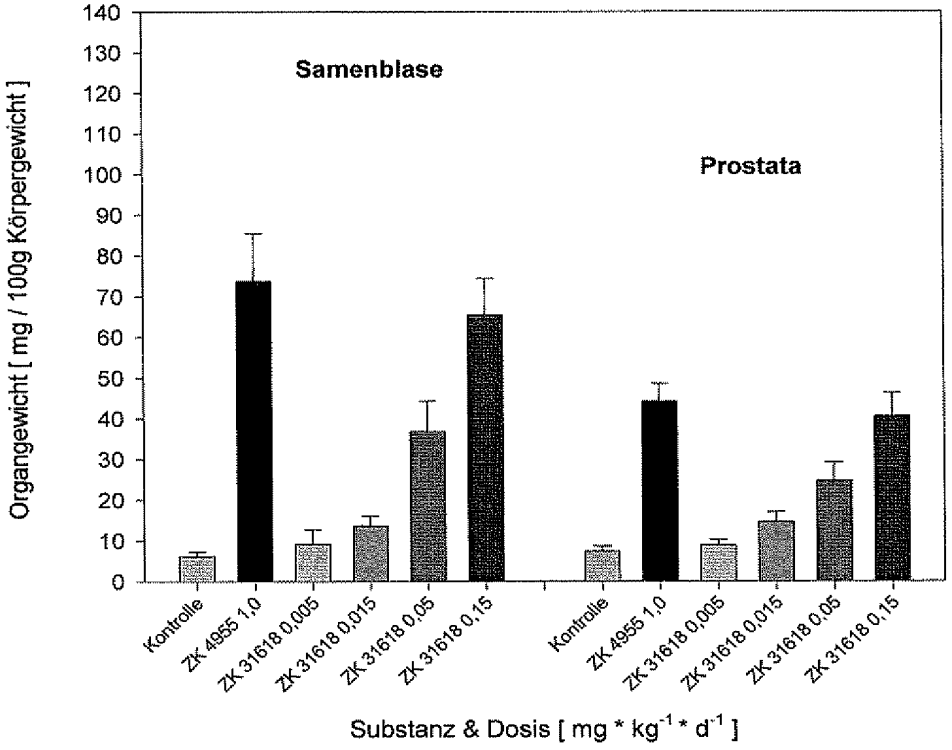
Klein/FKHT
01.11.00

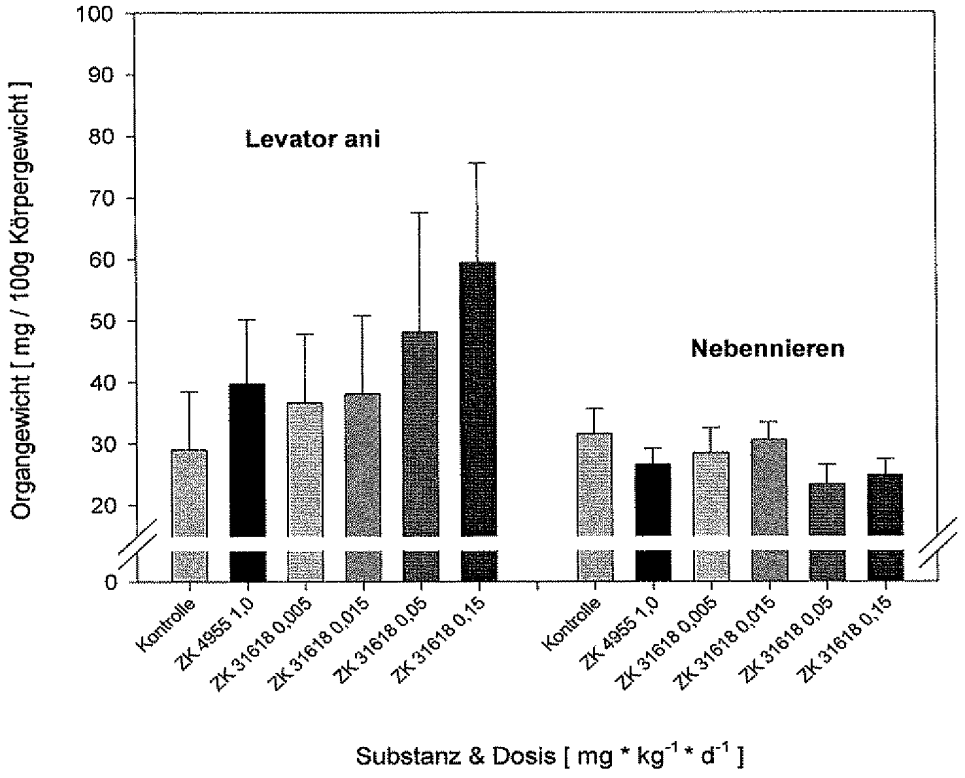
Schering AG
Research

GF 2000.0487

Graphische Darstellung der rel.Organgewichte vom Androgentest

(MENT)

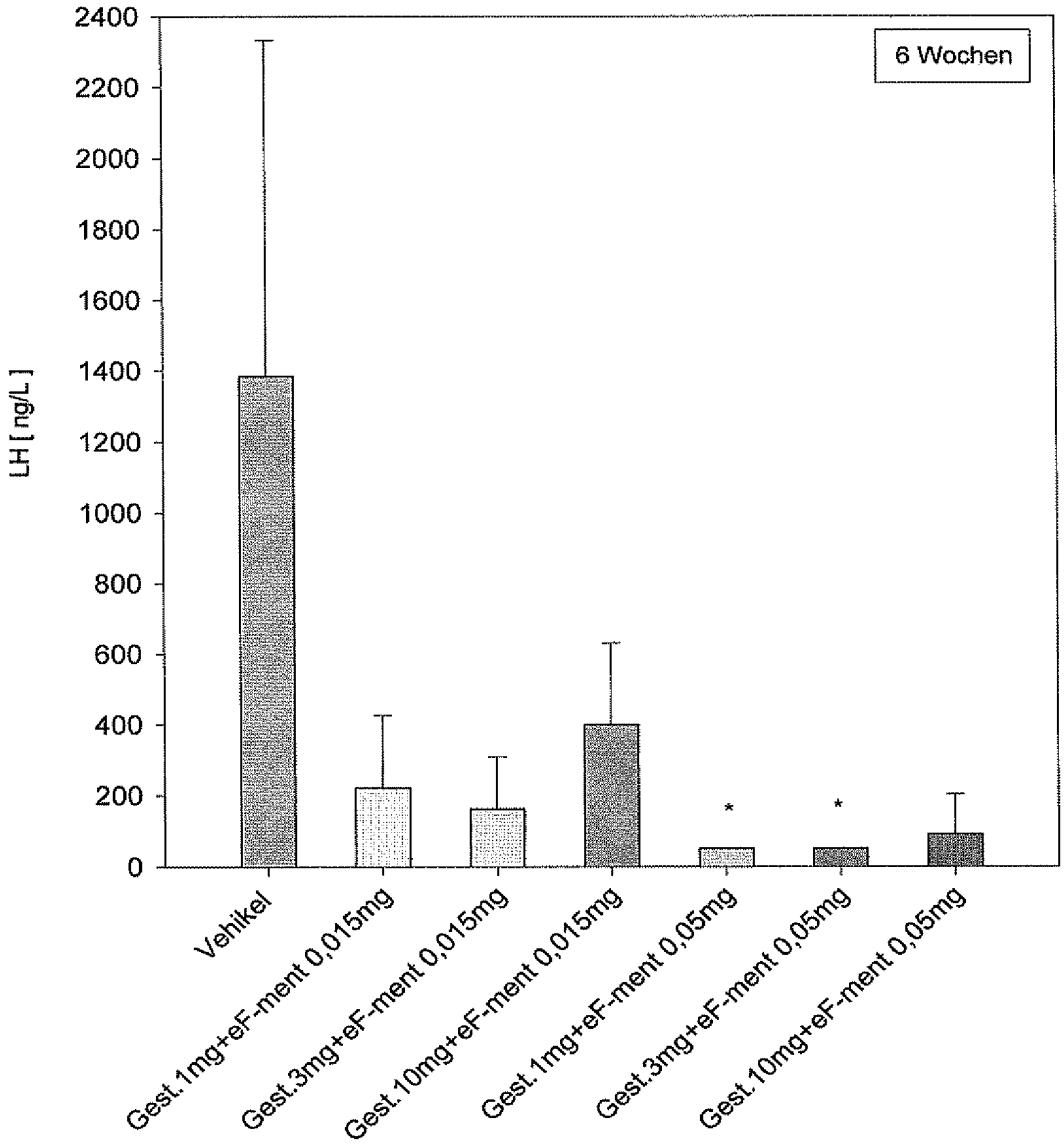




Efiloglu/FKHT
28.11.02

GF 2002.356

Einfluß von ZK 187.226(Gestagen) in Komb. mit ZK 244.312(eF-Ment) auf die LH-Konzentration im Serum bei der männl. Ratte nach einem Behandlungszeitraum von 6 Wochen bei s.c. Applikation



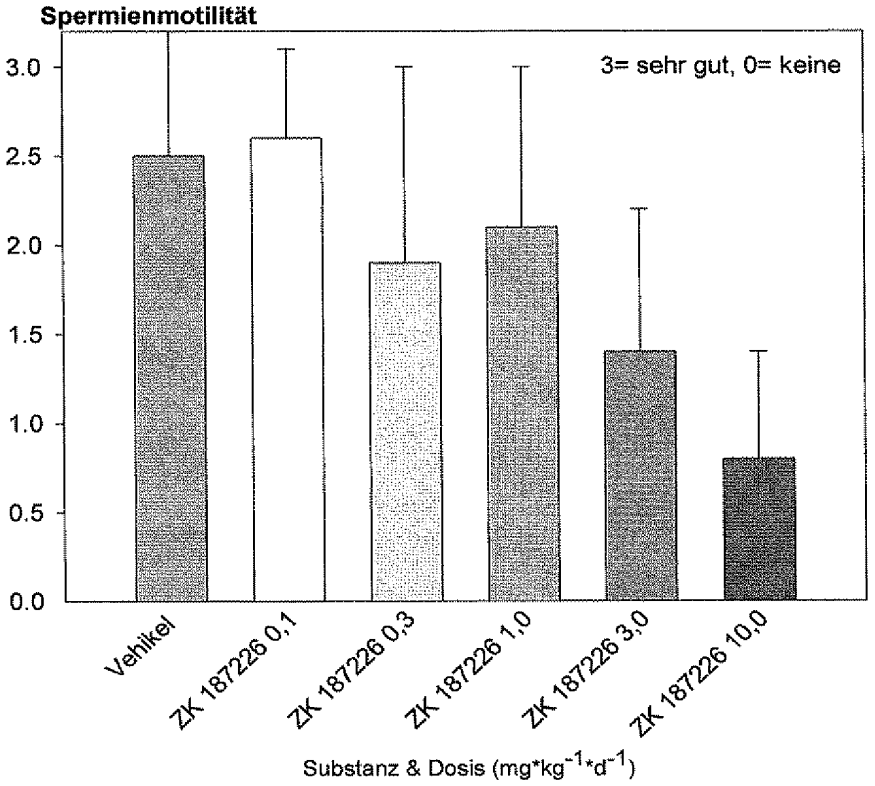
* alle Werte unter der Nachweisgrenze/halbe Nachweisgrenze berechnet und dargestellt

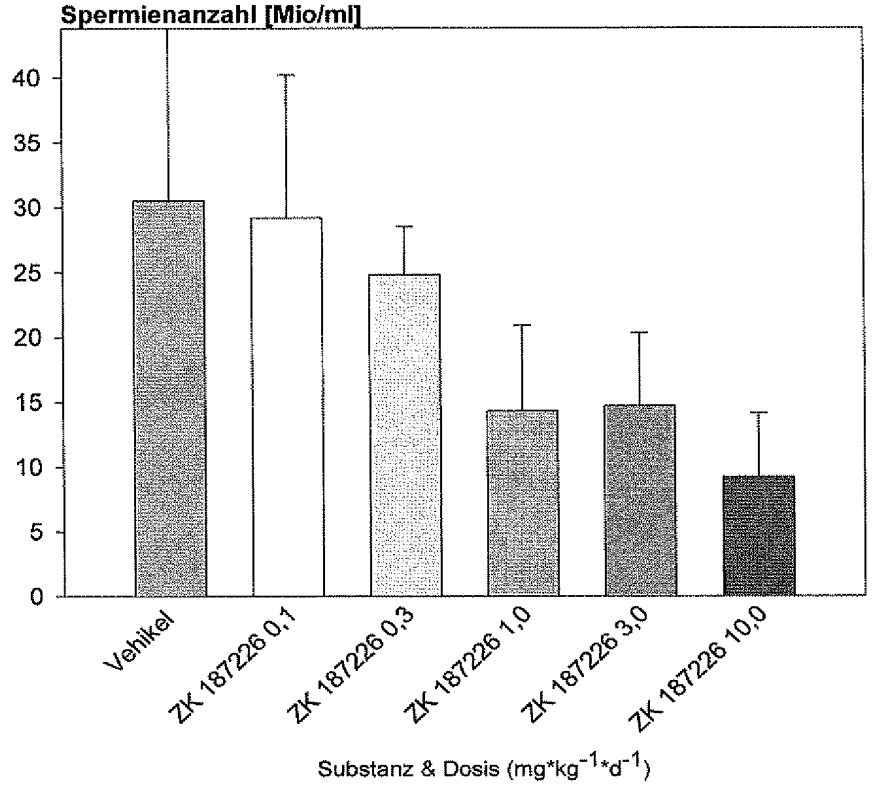
Marin
FKHT 08.12.99

GF 1999.0611

Schering AG
Research

Graphische Darstellung der Spermienmotilität und Anzahl vom Spermatogenesetest (ZK 187226)



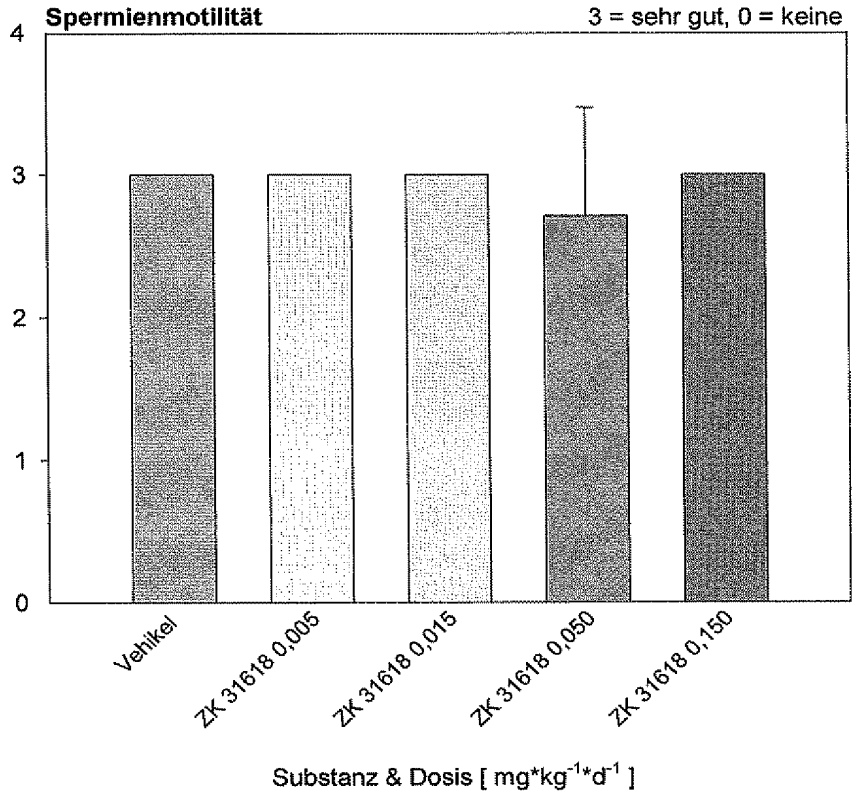


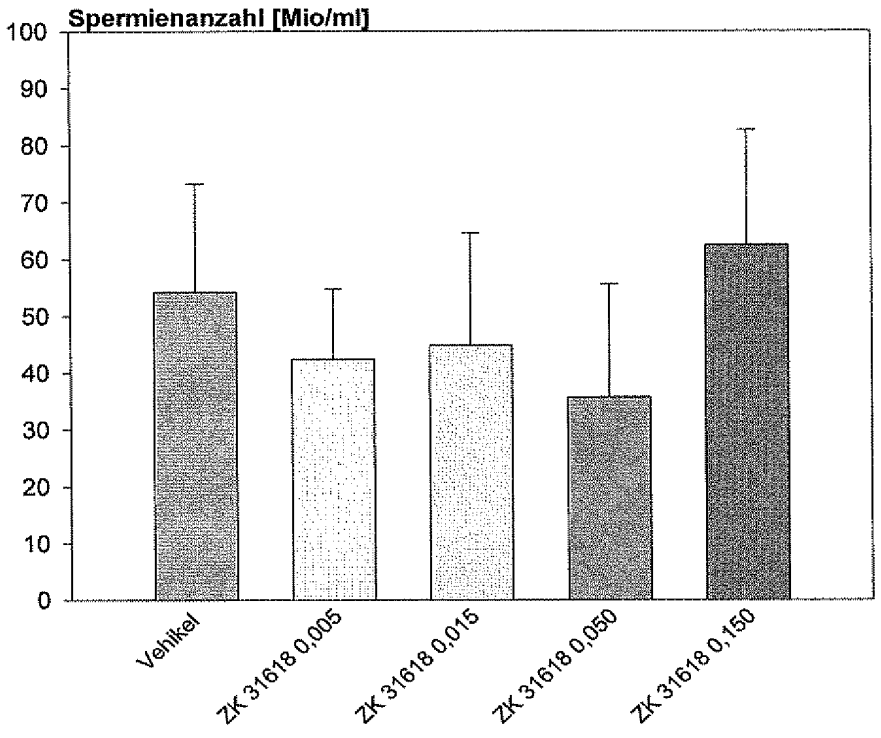
Klein / FKHT
28.03.2001

GF 2001.0006

Schering AG
Research

Graphische Darstellung der Spermienmotilität und Anzahl vom Spermatogenesetest (ZK 31618)

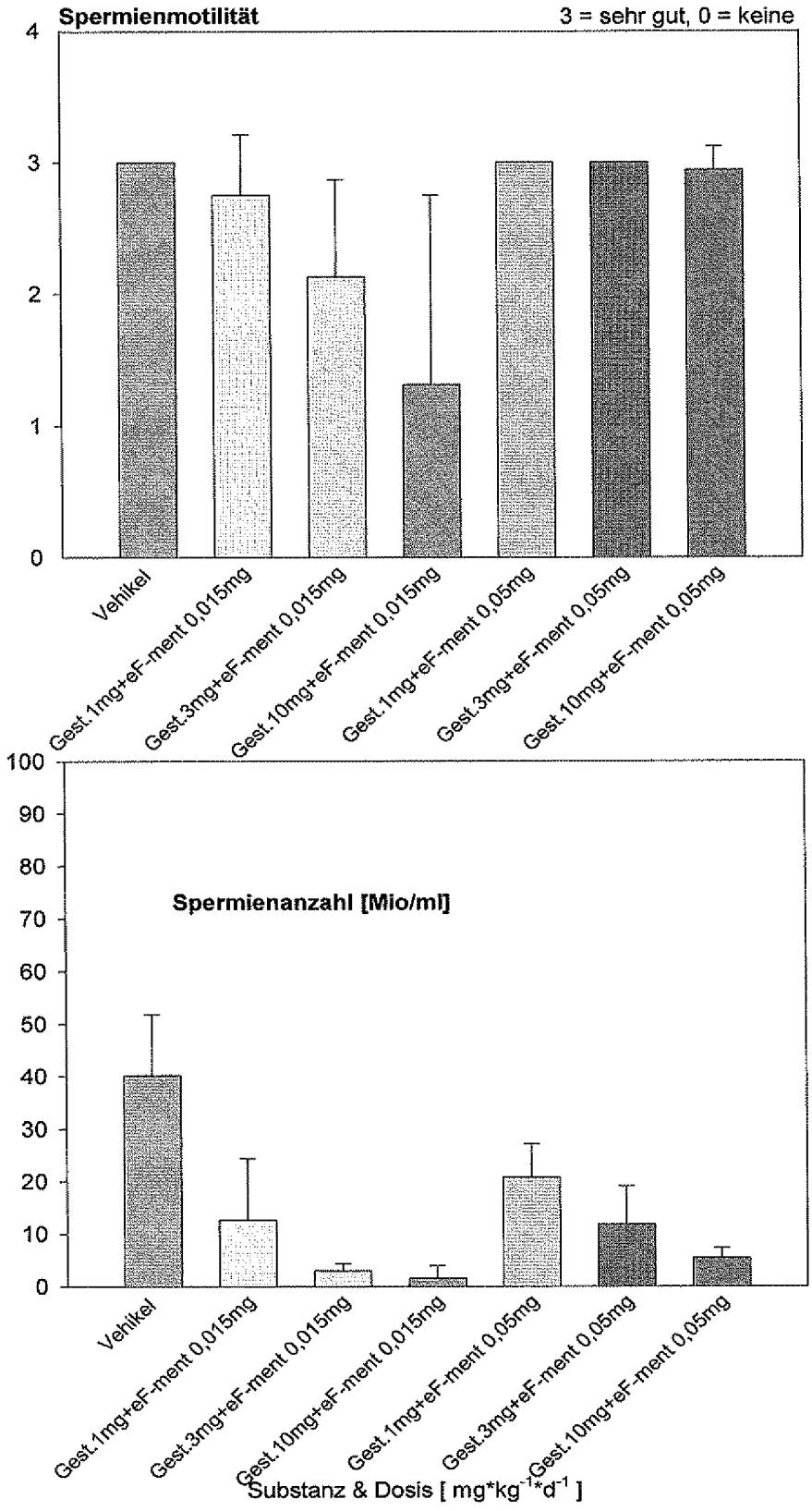




Efiloglu / FKHT
10.10.2002

GF 2002.0356

Graphische Darstellung der Spermienmotilität und Anzahl vom Spermatogenesetest (ZK 187.226+ZK 244.312))



Curriculum Vitae

Personal information

Surname(s) / First name(s)	**Nubbemeyer Reinhard Joachim**
Address(es)	9 Wilhelmstr., 13467 Berlin, Germany
E-mail	Reinhard.nubbemeyer@bayerhealthcare.com
Nationality	German
Date of birth	15.06.1963

Work experience

2003 onwards

Research Scientist, Research Pharmacokinetics, Bayer Schering Pharma AG, Berlin, Germany

Main activities and responsibilities

- Provide project support as study director for in silico, in vitro & in vivo studies (predominantly rodents but some non-rodents too)
- Responsible for method development and evalution with focus on in vivo (e.g. Accusampler)
- Analysis and documentation of research results, give internal and external presentations, strategy development in research PK, and act as a scientific reviewer
- Manage 3 technicians

October 1998 - December 2002

Research Scientist, Andrology, Schering AG, Berlin, Germany

Main activities and responsibilities

- Project leader of projects in Andrology
- Provide project support as scientist in in vivo pharmacology
- Generation of new projects in Andrology
- Responsible for method development and evalution, focus in vivo pharmacology (e.g. test of spermatogenesis)
- Analysis and documentation of research results, give internal and external presentations, act as a scientific reviewer
- Manage up to 5 technicians

1997 - 1998

Self-employment: regional authority Westfalia-Lippe, department museum education, Münster, Germany

- Teaching of children, adolescents and young adults in educational programs with reference to current exhibitions (e.g. dinosaurs, plains indians, mammals of Germany, human evolution)
- Revise scientific part of educational programs (human evolution)

Education and training

1995 - 1996

PostDoc, German Primate Center Göttingen, Germany

Principal subjects/occupational skills covered

Topic of the work: "Reproductive efficiency in the common marmoset (*Callithrix jacchus*)". Special knowledge in real time ultrasonography

1990 - 1994	
Title of qualification awarded	PhD (Dr. rer. nat.), Westfalian University of Münster, Germany
Principal subjects/occupational skills covered	Title of the thesis: "Biology and reproduction of the common vole (*Microtus arvalis*)". Focus on reproductive biology and metabolism.
1983 - 1989	
	Diploma (Dipl. Biol.), Georg-August University of Göttingen, Germany
Principal subjects/occupational skills covered	Title of the diploma work: "Method development: urnary diagnostics in the fallow deer (*Cervus dama*)". Construction and evaluation of a metabolic cage for fallow deer

Additional information

Publications (reviewed)

(1) Nubbemeyer, R.; Heistermann, M.; Oerke, A.-K. & Hodges, J. K. (1997). Reproductive efficiency in the common marmoset (*Callithrix jacchus*): A longitudinal study from ovulation to birth monitored by ultrasonography. Journal of Medical Primatology 26 (3): 139 –146.

(2) Morrell, J. M.; Nubbemeyer, R.; Heistermann, M.; Rosenbusch, J.; Küderling, I.; Holt, W. & Hodges, J. K. (1998). Artificial insemination in *Callithrix jacchus* using fresh or cryopreserved sperm. Animal Reproduction Science 52 (2):165-74.

(3) Nubbemeyer, R. (1999). Progesterone and testosterone concentrations during oestrus cycle and pregnancy in the common vole (*Microtus arvalis* Pallas); Comparative Biochemistry and Physiology A 122 (4): 437-444.

(4) Einspanier, A., Nubbemeyer, R., Schlote, S., Schumacher, M., Ivell, R., Fuhrmann, K., Marten, A. (1999). Relaxin in the marmoset monkey: secretion pattern in the ovarian cycle and early pregnancy. Biology of Reproduction 61: 512-520.

(5) Davies, B., Baumann, C., Kirchhoff, C., Ivell, R., Nubbemeyer, R., Habenicht, U. F., Theuring, F., Gottwald, U. (2004). Targeted deletion of the epididymal receptor HE6 results in fluid dysregulation and male infertility. Molecular and Cellular Biology 24(19):8642-8.

(6) Von Bonin, A., Buchmann, B., Bader, B., Rausch, A., Venstrom, K., Schäfer, M., Gründemann, S., Günther, J., Zorn, L., Nubbemeyer, R., Asadullah, K., Zollner, T.M. (2006). Efomycine M: an inhibitor of selectins? Nature Medicine 12 (8): 873.

(7) Otto, C., Rhode-Schulz, B., Schwarz, G., Fuchs, I., Klewer, M.,Brittain, D., Langer, G., Bader, B., Prelle, K., Nubbemeyer, R., Fritzemeier, K.-H. (2008). GPR30 localizes to the endoplasmic reticulum and is not activated by estradiol. Endocrinology. 2008 Oct;149(10):4846-56